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REC'D OCSPP TSCA CBIC
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Attention: Section 8(e) Coordinator
RE: Docket 8(e) HQ 99-14447

Dear Sir or Madam:

The International Institute of Synthetic Rubber Producers, Inc. (IISRP) has been sponsoring a cohort mortality study of nearly 18,000 male workers employed between 1943 and 1991 at eight styrene butadiene rubber (SBR) plants in the United States and Canada. IISRP reported to EPA on this study on a number of occasions including May 19, 1995 and June 26, 1995; the final report was submitted to this office on October 24, 1995. Additional studies were undertaken and reported to EPA in January and June of 2006, January 9, 2007 when we provided preliminary information on a companion study of nearly 4900 female SBR workers and then on July 20, 2007 the final report of the same study. On September 22, 2017 IISRP reported preliminary findings for an update of the SBR cohort and indicated final results would be published and submitted to the EPA. This letter provides the final manuscript accepted for publication and describes additional results for bladder cancer. IISRP's last submission to EPA was on November 15, 2017 in which we issued preliminary update study findings on the male cohort for nervous system disorders.

Today's submission conveys the final report which has been submitted and approved for publication. As indicated above, the report provides additional details regarding an excess of bladder cancer in hourly workers with long years worked. Internal analyses indicate positive exposure-response trends between both BD and styrene exposures and this cancer. Sparse data on bladder cancer from studies of other BD-exposed workers, inconsistent results across studies of other styrene-exposed populations, the paucity of investigations of bladder cancer incidence, rather than mortality, and UAB's inability to access possible confounding by smoking, limit the interpretation of their results for bladder cancer. More detail is contained in the manuscript as attached.

Should you have any questions please contact me at salinas@iisrp.com

Sincerely,

Juan Ramon Salinas Elizondo

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Managing Director and CEO
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Mortality among men and women in the North American synthetic rubber industry, 1943-2009

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Conflict of Interest: None Declared

Abstract

Objective: To evaluate 1943-2009 mortality among 22,785 synthetic rubber industry employees. Methods: Standardized mortality ratio (SMR) and internal Cox regression analyses. Results: Among hourly employees with ≥10 years worked and ≥20 years since hire, SMRs were elevated for leukemia (SMR=139, 95% confidence interval (CI)=106-179), non-Hodgkin lymphoma (NHL) (SMR=136, CI=102-177), bladder cancer (SMR=148, CI=110-195) and, for women only, lung cancer (SMR=225, CI=103-427). Butadiene and styrene exposure-response trends were positive for leukemia and bladder cancer but not for NHL or for lung cancer among women. Conclusions: Results support a causal relationship between butadiene and leukemia. Interpretation of results for lung cancer among women and for bladder cancer is uncertain because of inability to control for smoking and inadequate or inconsistent support from other studies for an association between butadiene or styrene and the latter cancers.

Key words

Keywords: 1,3 Butadiene; Styrene; synthetic rubber worker mortality; leukemia, non-hodgkin lymphoma, multiple myeloma

Introduction

Synthetic rubber manufacturing started in the United States (US) and Canada in the early 1940s, when 15 plants began operations. Approximately 70,000 workers have been employed in production jobs at some time in the industry in the US.[1] Styrene-butadiene rubber (SBR), a copolymer of 1,3-butadiene (BD) and styrene, has been the predominant type of synthetic rubber manufactured at these plants.

Workers in the synthetic rubber industry are exposed to several chemicals including BD and styrene monomers. BD is classified by the International Agency for Research on Cancer,[2–4] the National Toxicology Program and other agencies as a human carcinogen on the basis of epidemiologic results for lymphohematopoietic cancer (LHC), especially leukemia. The International Agency for Research on Cancer recently classified styrene as probably carcinogenic to humans (Group 2A), based on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals, and concluded that epidemiologic studies provide "credible evidence that exposure to styrene causes lymphohematopoietic malignancies, but confounding, bias or chance cannot be ruled out" as alternative explanations.[5] A committee of the National Research Council concluded that the evidence was limited, but credible, for an association between styrene and the risk of leukemia, non-Hodgkin lymphoma (NHL) and esophageal, pancreatic and kidney cancers.[6] Several studies of reinforced plastics industry workers, who had relatively high exposure to styrene, have reported excesses of lung cancer.[7–12] However, those excesses have not been attributed to styrene exposure, and one large study reported that styrene exposure in the Danish reinforced plastics industry was not associated with lung cancer.[13–15] Other investigations have suggested that styrene is a potential risk factor for bladder cancer,[15] sinonasal adenocarcinoma,[16] non-malignant respiratory disease (NMRD)[17,18] and nervous system disease.[5,10,17,19]

We previously assembled and analyzed epidemiologic data on 17,924 men and 4,863 women employed in the North American synthetic rubber industry. Our research on these employees indicated that male workers had an excess of leukemia that was likely to have been due to exposure to BD or BD plus other chemicals[20–29] and that women in the industry experienced excess mortality from lung and bladder cancers but not from leukemia or other forms of LHC.[30,31] The interpretation of the increased mortality from lung and bladder cancers observed among women was unclear because we could not determine that confounding by smoking fully explained the observed excess of lung cancer, and results for bladder cancer were based on small numbers.

In the above research, follow-up ended in 1998 for men[26] and in 2002 for women.[31] The present study compared the mortality rates of these workers, updated through 2009, with general population rates and evaluated mortality patterns by time since hire, work duration and estimated exposure to BD or styrene. Outcomes of special interest included deaths from LHC; cancers of the sinonasal passages, esophagus, pancreas, lung, kidney and bladder; and NMRD and nonmalignant nervous system disease. We previously presented updated exposure-response analyses of LHC in relation to cumulative exposure to BD and styrene for men, only.[29]

Methods

Earlier publications described plant operations and methods used to identify subjects, to develop work histories, to estimate exposure to BD and styrene and to determine vital status for the follow up period of 1944-1998 for men[24,26] and 1943-2002 for women.[31] The most recent prior updates included 17,924 men classified as having worked, before 1 January 1992, for at least one year at any of eight synthetic rubber plants, seven in the US and one in Canada;[26] and 4,863 women classified as having worked, before 1 January 1992, for at least one day at any of the eight study plants.[31] The current update included 17,924 men and 4,861

women. From the previously identified cohort of 4,863 women, we excluded two subjects who were found to be men and had also been included in the male cohort.

Information available from earlier studies included name, Social Security number (for US subjects), birth date, race, vital status as of the end of 1998 (men) or 2002 (women) and for decedents, death date and cause of death. Work histories and BD and styrene exposure estimates were available through the end of 1991. We did not obtain any additional work history information for 3,763 male and 480 female subjects who were actively working as of the end of 1991; exposures were relatively low after this time.

Work histories provided information on each job held by a subject, including the start and end dates, a text description of the work area and job, and the payroll classification (hourly or salaried) of the position. For employees at the six plants where work histories were available in sufficient detail, we developed quantitative estimates of each worker's exposure to BD and styrene.[24] Exposure estimation entailed identifying for each plant-specific work area/job combination its component tasks that involved exposure and documenting historical changes in those tasks; calculating plant-, work area/job- and time-specific average exposure indices (8-hour time-weighted average concentration in parts per million, ppm) and compiling these into job-exposure matrices (JEMs); and linking the time- and work area/job-specific exposure estimates in the JEMs with each employee's work history to obtain cumulative exposure estimates, as well as dates of first exposure to BD and styrene.

Our previous investigations identified 7,435 subjects (men, N=6,237; women, N=1,198) as deceased, 14,648 as presumed living (men, N=11,117; women, N=3,531) and 704 (men, N=570; women, N=134) as having unknown vital status.[26,31] The present study updated vital status information through 2009 for US workers by performing linkages with data from the Social Security Administration, Pension Benefits Inc. and the National Death Index (NDI), and we linked the Canadian cohort with the national Canadian Mortality Data

Base (CMDB) of Statistics Canada, supplemented with annual tax files (without income information). Using the above linkages, we established the vital status of 99% of the cohort. Only 286 workers (men, N=158; women, N=128) were lost to follow up. In addition to newly identified decedents in the expanded follow-up period, we identified four new male decedents with dates of death before 1999 and four female decedents with dates of death before 2003 who were previously classified as having unknown vital status.

For US employees, we used death certificates and International Classification of Diseases (ICD) codes from the NDI to determine their underlying cause of death. As part of this update, we attempted to obtain death certificates from state bureaus of vital records for US workers previously identified as deceased but with no cause of death information and were able to add cause of death information for 16 men and six women who previously had an unknown cause of death. Cause of death codes for Canadian decedents came from the CMDB. All codes for US and Canadian decedents were based on the revision of the ICD in effect at the time of death.

We compared workers' mortality rates to the rates of the male and female general populations of the states where the US plants were located (Texas, Kentucky or Louisiana) (US employees) or to the rates of the male and female general populations of Ontario (Canadian employees), using the standardized mortality ratio (SMR) as the measure of association. For SMR analyses of causes of death other than lymphoid and myeloid leukemia, the beginning of follow-up varied by plant from 1943/1944-1965, depending on the availability of employment records, and ended on 31 December 2009. For SMR analyses of lymphoid leukemia and myeloid leukemia, the maximum follow up-period was 1968 through 2009 for US subjects and 1969 through 2009 for Canadian subjects. Before these time periods, the ICD coding system used for general population rates combined acute lymphoid, acute myeloid, and other acute forms of leukemia into a single category.

We used the Occupational Mortality Analysis Program (OCMAP) to compute SMRs and their 95% confidence intervals (CIs) for all employees combined and for subgroups specified by employment factors.[32] Employment factors included payroll status (ever versus never hourly); duration of employment, computed until the date of last known employment; time since hire, computed based on the start date of employment in the industry; history of any exposure to BD, and history of any exposure to styrene. The SMR for a particular cause of death was the ratio (x100) of the number of deaths observed among workers to the number expected based on the cause-, plant-, race-, age-, sex- and calendar time-specific mortality rates of state or Ontario general populations. Throughout this report, we considered 95% CIs that did not include the SMR's null value of 100 as statistically significant.

Internal analyses, performed for selected diseases of interest, used Cox regression procedures to estimate hazard ratios (HRs) for workers ever versus never exposed to BD and ever versus never exposed to styrene and to assess exposure-response trends. These analyses treated BD and styrene ppm-years as time-dependent, used age as of each person-day of follow-up as the time scale and also adjusted for hire year, hire age, plant, race, gender and payroll status. The Cox regression models provided maximum partial likelihood estimates of disease-specific HRs (interpreted as rate ratios, RRs) for any versus no monomer exposure and examined trends in exposure-response using continuous BD or styrene ppm-years. Preliminary models evaluated possible interaction between monomer exposure and gender. We mention the results of those models only when a statistically significant interaction led us to fit separate models for women and men. For each disease examined in internal analyses, events included any decedent with the condition as the underlying or a contributing cause of death or with a medical record indicating that the condition was present. In the most recent prior update of our study of men, we obtained medical records of decedents whose death

certificate mentioned any type of lymphohematopoietic cancer.[28] We did not obtain any additional medical records for the current update.

Results

The total cohort of 22,785 workers included 17,924 (79%) men and 4,861 (21%) women (Table 1). Most men (15,010, 84%) had worked as hourly paid employees, whereas most women (3,418, 70%) had never been hourly. The median plant hire year was 1958, and workers had a median of 7.9 years of employment as of the end of 1991; men had worked longer than women (median: men, 11.4 years; women, 1.6 years). As of the end of 2009, the median time since hire was 40 years for the total cohort (men, 39 years; women, 44 years); the median age was 69 years and was similar for men and women; and 47% of the cohort was deceased (men, 50%; women, 34%). Of the 21,094 workers who had been employed at one of the six plants for which monomer exposure estimates were developed, 14,009 (66%) were classified as ever exposed to BD, and 15,427 (73%) were classified as ever exposed to styrene. The proportion of employees classified as ever exposed to BD or styrene was higher for men (BD, 77%; styrene, 84%) than for women (BD, 26%; styrene, 31%).

The cohort accrued 866,558 person-years of follow up (Table 2). Compared to the previous most recent studies, [26,31] the present study increased the person-years of follow-up by 21% for men and 13% for women and added 2,721 deaths among men (44% increase) and 453 (38% increase) among women. The SMR for all causes of death combined was 87 (10,617 deaths, 95% CI=85-89) for the total cohort, indicating a 13% deficit of deaths among workers compared to state or provincial general population referent groups. Overall mortality was lower than expected both for men (8,962 deaths, SMR=87, 95% CI=85-89) and for women (1,655 deaths, SMR=86, 95% CI=82-90).

The total cohort had slightly elevated SMRs for bladder cancer (80 deaths observed, SMR=109, 95% CI=86-135), all leukemia (120 deaths, SMR=110, 95% CI=91-131),

lymphoid leukemia (33 deaths, SMR=111, 95% CI=77-157), myeloid leukemia (54 deaths, SMR=126, 95% CI=95-165) and multiple myeloma (56 deaths, SMR=105, 95% CI=79-136). SMRs were below the null value of 100 for NHL, Hodgkin lymphoma, cancers of the esophagus, pancreas, lung and kidney and NMRD. For nonmalignant diseases of the nervous system, the SMR was 107 (303 deaths, 95% CI=95-119).

For most specific cancers, NMRD and nervous system diseases, results for men were similar to those for the total cohort. Women had SMRs of 113 (133 deaths, 95% CI=95-134) for lung cancer, 152 (10 deaths, 95% CI=73-279) for bladder cancer and 121 (11 deaths, 95% CI=60-216) for multiple myeloma. Their SMRs were below the null value of 100 for leukemia, NHL and Hodgkin lymphoma. Differences in observed and expected numbers of deaths were small for other specific forms of cancer among women, and women had no excess of deaths from NMRD or nervous system disease.

Two male workers and one female worker died of cancer of the nasal cavities/sinuses. The expected number of deaths was unknown, as we did not obtain general population rates for this cancer site.

Table 3 displays results for hourly employees stratified by years worked (<10 or ≥10 years). The corresponding results for the total cohort and for never-hourly employees are available in supplemental Table S1 (http://links.lww.com/JOM/A605). Hourly employees who worked for at least 10 years had excesses of bladder cancer (52 deaths, SMR=142, 95% CI=106-186) and leukemia (66 deaths, SMR=139, 95% CI=107-176). Their SMRs were 144 (20 deaths, 95% CI=88-222) for lymphoid leukemia, 126 (23 deaths, 95% CI=80-189) for myeloid leukemia, 126 (55 deaths, 95% CI=95-165) for NHL and 111 (27 deaths, 95% CI=73-162) for multiple myeloma. In this subgroup, SMRs were close to or below the null for other cancers of special interest, NMRD and nervous system disease. These analyses did not indicate excessive mortality from any other cause of death.

Analyses of hourly employees stratified by years since hire (<20 or ≥20 years) (Table 4) indicated that those with ≥20 years since hire had an excess of bladder cancer (68 deaths, SMR=131, 95% CI=102-166) and SMRs of 112 (115 deaths, 95% CI=92-134) for pancreatic cancer, 116 (75 deaths, 95% CI=92-146) for NHL, 122 (84 deaths, 95% CI, 97-151) for all leukemia, 123 (26 deaths, 95% CI=80-181) for lymphoid leukemia, 125 (35 deaths, 95% CI=87-174) for myeloid leukemia, 101 (37 deaths, 95% CI=71-140) for multiple myeloma and 112 (198 deaths, 95% CI=97-129) for nervous system disease. Their SMRs were approximately at or below the null for other cancers of interest and for NMRD. Results for other cohort subgroups in these analyses were unremarkable, except for an excess of Hodgkin lymphoma (5 deaths, SMR=333, 95% CI=108-778) among never hourly workers with <20 years since hire (supplemental Table S2, http://links.lww.com/JOM/A606).

Table 5 presents results for cancers of interest, NMRD and nervous system disease among hourly employees, stratified both by years since hire and by years worked. The main purpose of these analyses was to determine if hourly workers with both longer years worked (≥10 years) and longer years since hire (≥20 years) had evidence of excess mortality from these diseases. Also, these analyses assessed whether the SMR for a particular cause of death increased with increasing length of employment among those with longer potential induction time. The subgroup with ≥10 years worked and ≥20 years since hire had SMRs of 118 (75 deaths, 95% CI=93-148) for pancreatic cancer, 148 (51 deaths, 95% CI=110-195) for bladder cancer, 136 (54 deaths, 95% CI=102-177) for NHL, 139 (60 deaths, 95% CI=106-179) for all leukemia, 149 (20 deaths, 95% CI=91-231) for lymphoid leukemia and 134 (23 deaths, 95% CI=85-201) for myeloid leukemia. For bladder cancer, most of the deaths and the excess mortality among ever-hourly employees with ≥10 years worked and ≥20 years since hire occurred in the subgroup with ≥30 years since hire (47 deaths, SMR=164, 95% CI=120-218) (data not presented in a table). No excess of other cancers included in Table 5 were evident

among workers with longer work duration and time since first employment. Also, hourly employees with ≥10 years worked and ≥20 years since hire had lower than expected mortality from NMRD (354 deaths, SMR=89, 95% CI=80-99) and did not have any notable excess of nervous system disorders (117 deaths, SMR=109, 95% CI=90-131) or other causes of death (data not displayed in a table). In the ≥20 years since hire subgroup, SMRs were higher for those with ≥10 years worked than for those with shorter employment for pancreatic cancer, bladder cancer, leukemia and NHL. Of the three employees reported to have died of sinonasal cancer, all were short-term (≤2 years) employees with ≥20 years since hire.

SMR and internal analyses by monomer exposure for employees at six of the eight study plants also were performed for diseases of *a priori* interest. Table 6 displays, for the same set of diseases included in Table 5, the number of deaths included in SMR analyses by monomer exposure (ever versus never exposed) at six plants, the number of decedents included in internal analyses of monomer exposure and the median cumulative exposure values of the latter groups of cases exposed to each monomer. Supplemental Table S3 (http://links.lww.com/JOM/A607) summarizes the source of information (death certificate underlying or contributing cause of death; medical record) identifying decedents with each outcome examined in internal analyses.

SMR analyses indicated that workers with any exposure to BD had more observed than expected deaths from all leukemia (SMR=123, 95% CI=99-152), lymphoid leukemia (SMR=117, 95% CI=74-176) and myeloid leukemia (SMR=132, 95% CI=93-183) (Table 7). Internal analyses found adjusted RRs for any exposure to BD of 1.39 (95% CI=0.87-2.21), 1.09 (95% CI=0.54-2.24) and 1.47 (95% CI=0.77-2.84) for all leukemia, lymphoid leukemia and myeloid leukemia, respectively, with a statistically significant positive exposure-response trend for all leukemia (p=0.014) and for lymphoid leukemia (p=0.007) but not for myeloid leukemia (p=0.602). Workers with any exposure to styrene had SMRs and RRs above the

null for leukemias, but the styrene exposure-response trend was statistically significant only for lymphoid leukemia (p=0.046). NHL and multiple myeloma were not associated with BD or styrene exposure in external or internal analyses. There were no apparent sex-monomer exposure interactions for any of the LHCs.

With the exception of bladder cancer and lung cancer among women, no association with monomer exposure was observed for other diseases of *a priori* interest (Tables 7 and 8). For bladder cancer, the SMR was 116 (95% CI=89-150) for workers with any exposure to BD, the corresponding RR for ever- compared to never BD-exposed was 1.36 (95% CI=0.78-2.38), and there was a positive exposure-response trend (p=0.0003) (Table 7). Bladder cancer results were similar for those ever exposed to styrene (SMR=113, 95% CI=87-146; RR=1.23, 95% CI=0.66-2.28; trend p=0.004) (Table 8). There was no indication of sex-monomer exposure interaction for bladder cancer.

For male and female workers combined, lung cancer SMRs were below the null for those ever exposed to BD (Table 7) or styrene (Table 8). However, lung cancer deaths were increased among women ever exposed to BD (54 deaths, SMR=202, 95% CI=152-264) or styrene (55 deaths, SMR=179, 95% CI=135-233). The corresponding RRs for any versus to no exposure also were above the null among women (BD: RR=1.97, 95% CI=1.33-2.90; styrene: RR=1.55, 95% CI=1.01-2.37). However, no trend of increasing lung cancer risk with increasing exposure was evident for BD (trend p = 0.969) or styrene (trend p = 0.874). Deficits of lung cancer deaths occurred both among men ever exposed to BD (572 deaths, SMR=88, 95% CI=81-95) and among men ever exposed to styrene (628 deaths, SMR=90, 95% CI=83-97), and internal analyses found no association with lung cancer among men.

Numbers of cases of Hodgkin lymphoma (n=17) and sinonasal cancer (n=3) were too few to include in Cox regression analyses of monomer exposure. Of 17 Hodgkin lymphoma cases, nine were ever exposed to BD (median, 79 ppm-years), and 10 were ever exposed to

styrene (median, 4.9 years). All of the three sinonasal cancer cases were exposed to both BD (median, 16 ppm-years) and styrene (median, 2.9 ppm-years).

Discussion

The present cohort comprises the largest BD-exposed group studied to date and includes the only large group of BD-exposed women. The update substantially augmented information from our previous studies of male[20,26] and female synthetic rubber industry workers.[31] Compared to state or provincial general populations, employees had deficits of deaths from all causes combined and from most major causes of death. Workers' rates of death from circulatory, nonmalignant respiratory, digestive and genitourinary diseases and from external causes (i.e., accidents, homicides, and suicides) were lower than expected. These deficits tended to diminish as years since hire increased. This suggests that any confounding effect due to hiring relatively healthy people into the industry gradually disappeared.

Workers with long duration of employment and long time since hire had excesses of leukemia, NHL and bladder cancer but did not have excesses of other cancers of interest, including other LHCs and cancers of the esophagus, pancreas, lung and kidney, or from NMRD or nonmalignant nervous system disease. Positive monomer exposure-response trends were seen for leukemia, for bladder cancer and, among women only, for lung cancer. Only three deaths from sinonasal cancer occurred in the cohort.

LHC

Leukemia

The overall cohort had 10% more than expected deaths from leukemia compared to the general population. This excess was concentrated in hourly employees with ≥20 years since hire and ≥10 years worked, and internal analyses indicated an elevated rate of leukemia among workers ever versus never exposed to BD or styrene, with a positive and statistically significant exposure-response trend for both monomers. With regard to specific forms of

leukemia, results provided some evidence of an excess of both lymphoid and myeloid leukemia in the cohort subgroup with ≥20 years since hire and ≥10 years worked and among workers ever exposed to BD or styrene, but the trend of increasing risk with increasing cumulative exposure to monomers was statistically precise only for lymphoid leukemia.

The results of the present study for leukemia are consistent with those reported earlier by Santos-Burgoa et al.,[33] by Matanoski et al.[34,35] and by us[20,21,23] and add to the body of strong epidemiologic evidence of a positive association between exposure to BD and leukemia. Several experimental animal studies that have examined BD toxicokinetics, metabolism and genotoxicity provided strong evidence of the mechanism of carcinogenicity of BD.[2] Some, but not all, studies in humans have demonstrated genotoxicity.[36] Investigations of relatively small cohorts of BD monomer production workers, who were exposed to BD but not to styrene, have reported results for leukemia that were null or weakly positive.[37–39]

Increased risks of LHC, particularly leukemia and lymphoma, have been reported among styrene-exposed workers in both the reinforced plastics and synthetic rubber industries. In the synthetic rubber industry, BD and styrene exposures were highly correlated, and the individual effects of the two monomers could not be delineated. On the other hand, studies of reinforced plastics industry included workers who were exposed to styrene concentrations at higher levels than were typically found in the synthetic rubber industry, and reinforced plastics workers were not exposed to BD. Positive exposure-response relationships between styrene exposure and leukemia were reported in an older multinational European study among reinforced plastics workers,[14] but studies of several other cohorts of reinforced plastics workers did not provide strongly supportive evidence of an association between styrene and overall leukemia.[8,9,11] Collins and Delzell[40] in their recent meta-analyses of 13 studies found no association between styrene exposure and all leukemia.

With regard to exposure to BD or styrene and cell-type specific leukemias, data from other studies are limited. A recent investigation of workers exposed to styrene in the Danish reinforced plastics industry reported a positive association with myeloid leukemia and patterns of increasing standardized incidence ratios (SIRs) with increasing duration of employment (highest category, ≥10 years worked: SIR=1.56, 95% CI=0.98-2.36); lymphoid leukemia incidence also was increased among workers in the longest employment category (≥10 years worked: SIR=1.38, 95% CI=0.92-2.00).[11] A further analysis of the same cohort reported a positive exposure-response trend for the association between a styrene cumulative exposure score and acute myeloid leukemia when exposure was restricted to that occurring 15-29 years in the past.[41] A study of mortality among workers employed in the US reinforced plastics and composite industry reported a myeloid leukemia SMR of 1.27 (8 deaths, 95% CI=0.55-2.50) in the highest category of cumulative exposure to styrene, with no statistically significant exposure-response trend.[9] In their meta-analysis of 13 studies, Collins and Delzell,[40] found no association between styrene and lymphoid or myeloid leukemia. The most recent IARC review[5] noted increased incidence of or mortality from subtypes of leukemia, particularly acute myeloid leukemias, among styrene-exposed reinforced plastic's industry workers.

Lymphoma

The present study found that the overall cohort did not have an excess of NHL or multiple myeloma deaths, no association was demonstrated for workers ever exposed to monomers, and there were no exposure-response trends for cumulative exposure to either monomer. However, the cohort subgroup with ≥20 years since hire and ≥10 years worked had an excess of NHL similar to that observed in the same subgroup for leukemia. Our previous analyses of exposure-response patterns for NHL found little evidence of an association with

styrene, no association with BD and no association between either monomer and multiple myeloma.[29]

Several studies have assessed mortality from NHL or subtypes of NHL in three cohorts of BD monomer production workers who were exposed to BD but not to styrene.[37–39,42] Ward et al.[37,42] reported a statistically significant increase in deaths from lymphosarcoma and reticulosarcoma (a form of NHL), based on 4 observed compared to 0.69 expected deaths, in a cohort of 364 male BD monomer production workers. Tsai et al.[39] noted 1 observed versus 0.2 expected deaths from lymphosarcoma and reticulosarcoma in another small study of mortality among 614 men potentially exposed to BD at a refinery and a petrochemical plant. Divine and Hartman,[38] in a larger study of 2,800 male BD monomer production workers, reported 19 observed compared to 12.9 expected deaths from NHL, including 9 observed versus 4.4 expected deaths from lymphosarcoma. Although Divine and Hartman[38] did not find trends in the risk of NHL with duration of exposure or with estimated cumulative exposure to BD, the association was highest among BD monomer workers who had been exposed during the Second World War, when exposures were known to have been high.

Matanoski et al.[34] in an investigation that included many of the same subjects in our study, reported a positive association between styrene and NHL. In contrast, recently updated studies of reinforced plastics industry workers, exposed to styrene but not to BD, did not find a clear or statistically significant excess of NHL, overall or in subgroups with higher styrene exposure.[7–11,41]

Matanoski et al.[34] reported that multiple myeloma was associated with BD in a study that included most of the subjects in our male cohort, in contrast to our analyses by cumulative exposure, which provided no support for an association with BD or styrene exposure. Divine and Hartman[38] reported slightly more than expected deaths from multiple

myeloma among BD production workers. However, analyses of multiple myeloma in relation to estimated cumulative exposure to BD were not performed, and like this study's results for leukemia and NHL, the data on multiple myeloma were too sparse and too internally inconsistent to provide any substantial support for a causal interpretation. Collins and Delzell[40] in their meta-analysis found little support for a causal association between styrene and NHL or multiple myeloma.

On balance, this study found little evidence that exposures in the synthetic rubber industry cause NHL and found no association with multiple myeloma. Future analyses will examine BD and styrene exposure-response patterns for all B-cell malignant neoplasms combined, including chronic lymphoid leukemia, multiple myeloma and other forms of NHL.

No excess of Hodgkin lymphoma was found in our study. However, the small number of decedents with this cancer precluded detailed analyses.

Lung cancer

Women in this study had a 13% excess of lung cancer deaths, while men had a statistically significant deficit of deaths from this cancer. Analyses of monomer exposure found elevated SMRs and RRs for women, but not for men, ever exposed to BD or styrene. Among women, monomer exposure-response trends were not evident, and results of exposure-response analysis among men confirmed the lack of any association with BD or styrene.

Results of our previous analyses of lung cancer among women were not persuasive of a causal association with BD or styrene.[27] Other studies of BD-exposed workers, neither of which included women, have not reported an association with lung cancer.[38,39] One study of male and female styrene-exposed workers in the British reinforced plastics industry found significantly elevated mortality from lung cancer, and the magnitude of risk rose with increasing exposure categories, with an SMR of 144 (95% CI=110-186) in the highest

exposure category.[8] Other studies of styrene-exposed workers have reported elevated lung cancer SMRs but have not found any consistent evidence of a causal association between styrene and lung cancer.[6,7,43,44] Experimental studies have shown that styrene exposure causes lung tumors in several strains of mice, but not in rats.[45] The relevance to humans of the positive toxicological findings for lung tumors in mice has been questioned.[46]

The interpretation of the association with lung cancer among women seen in our study remains uncertain. Confounding by smoking may account in part for the elevated SMR for lung cancer among women, as we estimated in a previous study of the same women that indirect adjustment for smoking reduced the observed association between employment and lung cancer by 8% to 11%.[27] The lack of a positive exposure-response trend does not support a causal interpretation.

Bladder cancer

Increased bladder cancer mortality was seen among both men and women in the overall cohort. An excess of this cancer was particularly evident in hourly employees with 30 or more years since hire and 10 or more years of employment, and internal analyses further indicated a positive association with monomer exposure, with a statistically significant exposure-response trend both for BD and for styrene. Divine and Hartman [38] reported slightly fewer bladder cancer deaths than expected in their overall cohort of monomer industry workers (8 observed/10.9 expected), and approximately equal observed and expected numbers (4/3.9) in the subgroup employed for 20+ years, while Tsai et al.[39] did not report results for bladder cancer among workers potentially exposed to BD. An older European international mortality study of reinforced plastics workers found no association with bladder cancer mortality.[13–15] Several more recent mortality studies of workers exposed to styrene in this industry reported increases in bladder cancer deaths,[7–10] but a recent, large investigation of cancer incidence among Danish reinforced plastics workers found no association with

bladder cancer.[11] Workers in some rubber products manufacturing plants have an increased risk of bladder cancer because of their exposure to aromatic amines. To our knowledge, such exposure did not occur in the synthetic rubber industry. Cigarette smoking is an established cause of bladder cancer.[47] The association that we observed could be due to uncontrolled confounding by smoking, but we do not have data to support or refute this possibility.

Other cancers

We found no evidence of causal associations between synthetic rubber industry employment or monomer exposures and mortality from other cancers of interest with regard to styrene, including sinonasal, esophageal, pancreatic and kidney cancers. Thus, our study results do not strengthen the currently limited evidence for an association between occupational styrene exposure and these cancers.[5]

Nissen et al.[16] reported a five-fold increased risk of sinonasal adenocarcinoma following a high level of cumulative styrene exposure among Danish reinforced plastics industry workers, a result based on small numbers and unadjusted for wood dust exposure. Harris et al.[48] found no death from sinonasal cancer (1.2 expected) among workers in the British glass-reinforced plastics industry. We found three deaths from sinonasal cancer in the present study, but only one of these had worked briefly in an area with potential for high monomer exposure. In this study, information on histologic cell type was not available, and we do not know if any of the three decedents had adenocarcinoma. Thus, our results for sinonasal cancer do not support the finding of Nissen et al.[16]

Nervous system disease

The employees in this study had a small increase in deaths from nervous system disorders. This increase was restricted to men, occurred both in ever hourly and never hourly men and did not display a consistent pattern of increasing risk with increasing length of employment or with cumulative exposure to monomers. This cause of death category

includes Alzheimer's disease, whereas deaths from dementia are classified in another cause of death category, mental disorders, for which we observed a statistically significant deficit of deaths. Previous research[10,17,19] suggests that exposure to styrene may contribute to nervous system diseases. Further, Ruder et al.[10] found a styrene-associated excess risk of neurodegenerative disease subcategories including Alzheimer's diseases, cerebrovascular dementia and amyotrophic lateral sclerosis. We found little evidence of an association with workplace exposures. It is possible that the small excess of nervous system disease deaths was due to differential misclassification of these causes of death.

NMRD

The overall cohort in our study and all subgroups had deficits of deaths from NMRD. Internal analyses found no clear evidence of an association with styrene, while for BD the exposure-response trend was of borderline statistical significance. A recent review has suggested that occupational exposure to styrene is a potential risk factor for NMRD.[16] However, cohort studies of reinforced plastic workers are inconsistent in their results, with most reporting negative or nonsignificant associations. Only one study by Collins et al.[9] reported a slight excess of deaths from NMRD that was statistically significant for the overall cohort and in the subgroup with 15 or more years since hire; however, there was no exposure-response trend. Divine and Hartman[38] and Tsai et al.[39] found approximately equal observed and expected deaths from NMRD in the monomer industry (Divine and Hartman: 128 observed/129 expected deaths, SMR=99, 95% CI=83-118; Tsai et al.: 36/37, SMR=98, 95% CI=68-135).

Strengths and limitations

The main strengths of the study were its long-term follow-up period, minimal losses to follow-up, use of objective procedures for classifying workers according to various indices of exposure and to cause of death, inclusion of female employees and evaluation of mortality

patterns by a number of employment factors, including cumulative exposure to monomers. Limitations included the lack of information on lifestyle factors, most importantly cigarette smoking. Misclassification by cause of death and by employment or exposure variables is another potential problem. We used exposure and outcome classification procedures that were objective, so that any misclassification would tend to be nondifferential. The study also was limited by its reliance on mortality data for ascertainment of outcomes, rather than using disease incidence data. The mortality end point is not optimal for certain cancers and other diseases associated with relatively long survival such as bladder cancer and certain forms of leukemia. Our internal analyses of monomer exposure, which included cases identified from multiple sources rather than from underlying cause of death data only, minimized, but did not eliminate, this limitation.

Conclusions

The results of this study add to the body of epidemiologic evidence of a positive association between exposure to BD and leukemia, with the current support being somewhat stronger for a causal relationship with lymphoid than with myeloid leukemia. External support for an association between styrene and leukemia is weaker. Hourly workers with relatively long years of employment and years since hire had an excess of NHL similar in magnitude to that seen for leukemia, but we found no exposure-response association between either NHL or multiple myeloma and BD or styrene. Female synthetic rubber industry workers and those exposed to monomers had more than expected deaths from lung cancer. However, internal analyses did not provide clear support for a causal association between monomer exposure and lung cancer among women, and employment variables including monomer exposure were not associated with lung cancer among men. Hourly workers with long years worked and years since hire had an excess of bladder cancer deaths, and internal analyses indicated positive exposure-response trends between both BD and styrene exposures

and this cancer. Sparse data on bladder cancer from studies of other BD-exposed workers, inconsistent results across studies of other styrene-exposed populations, the paucity of investigations of bladder cancer incidence, rather than mortality, and our inability to assess possible confounding by smoking limit the interpretation of our results for bladder cancer. Other results were not indicative of a causal association between occupational factors and any of the cancers of *a priori* interest, NMRD or nonmalignant nervous system disease.

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Table 1. Number of subjects by selected characteristics for men (1944-2009) and women (1943-2009) and all subjects combined*

	All subjects	Men	Women
	N (%)	N (%)	N (%)
	22,785 (100)	17,924 (100)	4,861 (100)
Plant, location, follow-up start year†			
1, Kentucky, 1965, 1965	1,563 (7)	1,391 (8)	172 (3)
2, Texas, 1944, 1943	1,057 (5)	776 (4)	281 (6)
3, Louisiana, 1944, 1943	2,464 (10)	1,989 (11)	475 (10)
4, Louisiana, 1944, 1943	2,849 (12)	2,084 (12)	765 (16)
5, Texas, 1960, 1965	634 (3)	563 (3)	71 (1)
6, Texas, 1944, 1943	2,930 (13)	2,328 (13)	602 (12)
7, Ontario, 1950, 1950	7,044 (31)	5,356 (30)	1,688 (35)
8, Texas, 1944, 1943	4,244 (19)	3,437 (19)	807 (17)
Payroll status			
Ever hourly	16,453 (72)	15,010 (84)	1,443 (30)
Never hourly	6,332 (28)	2,914 (16)	3,418 (70)
Years worked as of the end of 1991			
< 10	12,363 (54)	8,309 (46)	4,054 (83)
10-19	4,344 (19)	3,865 (22)	479 (10)
20+	6,078 (27)	5,750 (32)	328 (7)
Median	7.9	11.4	1.6
Year of hire			
< 1950	6,143 (27)	4,656 (26)	1,487 (31)
1950-1959	5,929 (26)	4,900 (27)	1,029 (21)
1960-1969	4,678 (21)	3,757 (21)	921 (19)
1970+	6,035 (26)	4,611 (26)	1,424 (29)
Median	1958	1958	1959
Years since hire			
< 20	1,602 (7)	1,340 (7)	262 (5)
20-29	3,871 (17)	3,218 (18)	653 (14)
30+	17,312 (76)	13,366 (75)	3,946 (81)
Median	40.1	39.4	43.7
Vital Status			
Alive	11,882 (52)	8,804 (49)	3,078 (63)
Deceased	10,617 (47)	8,962 (50)	1,655 (34)
Unknown	286 (1)	158 (1)	128 (3)
Age at end of study			
<60	6,024 (26)	4,782 (27)	1,242 (25)
60-69	6,062 (27)	4,842 (27)	1,220 (25)
70-79	6,330 (28)	5,129 (28)	1,201 (25)
80+	4,369 (19)	3,171 (18)	1,198 (25)
Median	68.9	68.7	69.7
Butadiene‡			
Ever exposed, N (%)	14,009 (66%)	12,819 (77%)	1,190 (26%)
Styrene‡			
Ever exposed, N (%)	15,427 (73%)	14,011 (84%)	1,416 (31%)

*Results used data as of the end of 2009 except years worked, which were determined as of 1991 because work histories were not obtained after 1991.

†The first year pertains to men and the second, to women.

‡Data limited to subjects in six plants with exposure estimates. Percentages are calculated as proportions of all workers at the six plants (1,3,4 6-8); men, n=16,585, women, n=4,509.

Table 2. Observed number of deaths (D), standardized mortality ratio (SMR) and 95% confidence interval (CI) by cause of death for all workers, men (follow-up, 1944-2009) and women (follow-up, 1943-2009), 8 plants

	Total		Men		Women	
	(PY[†]=866,558)		(PY=661,346)		(PY=205,212)	
Cause	D	SMR	D	SMR	D	SMR
All causes	10617	87 (85-89)	8962	87 (85-89)	1655	86 (82-90)
All cancer	2892	93 (90-97)	2407	93 (89-97)	485	94 (86-102)
Buccal cavity & pharynx	44	64 (46-85)	38	60 (43-83)	6	97 (36-211)
Esophagus	71	91 (71-114)	66	90 (70-115)	5	96 (31-224)
Stomach	94	85 (69-104)	88	90 (72-110)	6	50 (19-110)
Colorectum	298	96 (85-107)	264	101 (90-115)	34	66 (46-92)
Liver	70	83 (65-105)	57	80 (61-104)	13	102 (54-174)
Pancreas	152	96 (82-113)	129	99 (83-118)	23	84 (53-126)
Larynx	18	51 (30-81)	18	54 (32-85)	0	0 (0-217)
Lung	923	91 (85-97)	790	88 (82-95)	133	113 (95-134)
Bladder	80	109 (86-135)	70	104 (81-132)	10	152 (73-279)
Kidney	65	90 (69-114)	61	97 (74-124)	4	43 (12-111)
Brain	66	97 (75-123)	59	105 (80-135)	7	59 (24-121)
Prostate	250	105 (92-119)	250	105 (92-119)	0	()
Breast	97	103 (83-125)	3	97 (20-283)	94	103 (83-126)
Uterus	11	42 (21-75)	0		11	42 (21-75)
Ovary	25	88 (57-130)	0		25	88 (57-130)
Non-Hodgkin lymphoma	95	92 (75-113)	78	93 (73-116)	17	90 (52-144)
Hodgkin lymphoma	13	91 (48-155)	12	97 (50-169)	1	50 (1-279)
Leukemia	120	110 (91-131)	106	114 (94-138)	14	83 (46-140)
Lymphoid[*]	33	111 (77-157)	29	113 (76-162)	4	103 (28-263)
Myeloid[*]	54	126 (95-165)	47	133 (98-177)	7	95 (38-195)
Multiple myeloma	56	105 (79-136)	45	102 (74-136)	11	121 (60-216)
Other cancer	344	93 (84-104)	276	90 (79-101)	71	113 (88-143)
Benign neoplasms	19	83 (50-130)	18	102 (60-161)	1	19 (0-107)
Blood disorders	35	89 (62-124)	30	96 (65-138)	5	62 (20-144)
Mental disorders	111	65 (54-79)	81	63 (50-79)	30	72 (48-102)
Allergic, endocrine & metabolic disease	268	68 (60-77)	225	73 (64-83)	43	50 (36-68)
Nervous system disease	303	107 (95-119)	237	111 (97-126)	66	94 (73-120)
Circulatory disease	4624	90 (87-93)	3988	91 (88-94)	636	85 (79-92)
Nonmalignant respiratory disease	765	81 (75-87)	618	78 (72-85)	147	94 (79-110)
Digestive disease	322	67 (60-75)	270	67 (59-75)	52	68 (51-89)
Genitourinary disease	179	73 (63-85)	144	73 (62-86)	35	75 (52-104)
External causes	642	73 (68-79)	565	72 (66-78)	77	92 (73-115)
Other known	457	87 (79-95)	379	88 (80-98)	78	82 (65-102)
Unknown	128		112		16	

[*]Lymphoid and myeloid leukemia: follow-up period, 1968/1969-2009.
[†]PY, person-years.

Table 3. Observed number of deaths (D), standardized mortality ratio (SMR) and 95% confidence interval (CI) by cause of death, years worked, ever hourly, for men and women combined (1943/1944-2009), 8 plants

	Worked <10 years		Worked ≥10 years	
	Ever hourly		Ever hourly	
	(PY[†]=346,768)		(PY=262,724)	
Cause	D	SMR (95% CI)	D	SMR (95% CI)
All causes	3545	90 (87-93)	4927	92 (90-95)
All cancer	892	97 (91-104)	1377	99 (94-105)
Buccal cavity & pharynx	11	51 (26-92)	22	66 (42-101)
Esophagus	19	81 (49-126)	39	99 (71-136)
Stomach	34	96 (66-133)	49	93 (69-123)
Colorectum	80	89 (71-111)	152	106 (90-125)
Liver	27	102 (67-148)	24	66 (42-98)
Pancreas	44	93 (67-124)	76	109 (86-136)
Larynx	5	47 (15-110)	12	67 (35-117)
Lung	324	111 (99-124)	448	93 (85-102)
Bladder	18	88 (52-139)	52	142 (106-186)
Kidney	23	106 (67-158)	28	86 (57-124)
Brain	19	89 (54-139)	30	108 (73-155)
Prostate	79	120 (95-149)	130	98 (82-116)
Breast	25	101 (66-149)	3	57 (12-165)
Uterus	5	56 (18-131)	2	200 (24-722)
Ovary	7	97 (39-200)	2	167 (20-602)
Non-Hodgkin lymphoma	21	69 (43-106)	55	126 (95-165)
Hodgkin lymphoma	3	53 (11-154)	4	77 (21-197)
Leukemia	30	89 (60-127)	66	139 (107-176)
Lymphoid[*]	7	84 (34-174)	20	144 (88-222)
Myeloid[*]	17	135 (79-216)	23	126 (80-189)
Multiple myeloma	13	83 (44-143)	27	111 (73-162)
Other cancer	105	92 (75-111)	156	99 (84-116)
Benign neoplasms	4	46 (13-118)	11	129 (65-232)
Blood disorders	14	108 (59-181)	14	87 (48-146)
Mental disorders	38	78 (55-108)	39	56 (40-77)
Allergic, endocrine & metabolic disease	82	66 (52-81)	138	84 (71-100)
Nervous system disease	91	111 (90-137)	120	106 (88-127)
Circulatory disease	1493	90 (86-95)	2264	97 (93-101)
Nonmalignant respiratory disease	240	86 (75-97)	363	86 (77-95)
Digestive disease	113	71 (58-85)	139	68 (57-81)
Genitourinary disease	57	68 (52-89)	92	90 (73-111)
External causes	306	79 (71-89)	238	76 (67-87)
Other known	215	114 (99-131)	132	63 (53-75)
Unknown		21 (16)		

[*]Lymphoid and myeloid leukemia: follow-up period, 1968/1969-2009.

[†]PY, person-years.

Table 4. Observed number of deaths (D), standardized mortality ratio (SMR) and 95% confidence interval (CI) by cause of death, years since hire and ever hourly, for men and women combined (1943/1944-2009), 8 plants

	<20 years since hire		≥20 years since hire	
	Ever hourly		Ever hourly	
	(PY[†]=293,589)		(PY=315,904)	
Cause	D	SMR (95% CI)	D	SMR (95% CI)
All causes	992	62 (58-66)	7480	97 (95-100)
All cancer	184	66 (57-76)	2085	103 (99-107)
Buccal cavity & pharynx	3	33 (7-95)	30	66 (45-94)
Esophagus	5	70 (23-164)	53	95 (71-125)
Stomach	15	78 (43-128)	68	99 (77-125)
Colorectum	20	76 (46-117)	212	103 (89-118)
Liver	2	31 (4-113)	49	86 (64-114)
Pancreas	5	35 (12-83)	115	112 (92-134)
Larynx	3	79 (16-231)	14	57 (31-95)
Lung	62	81 (62-103)	710	102 (95-110)
Bladder	2	38 (5-139)	68	131 (102-166)
Kidney	4	61 (17-155)	47	98 (72-130)
Brain	5	49 (16-114)	44	113 (82-152)
Prostate	4	42 (11-107)	205	108 (94-124)
Breast	4	71 (19-183)	24	98 (63-146)
Uterus	1	34 (1-192)	6	87 (32-189)
Ovary	1	83 (2-464)	8	113 (49-222)
Non-Hodgkin lymphoma	1	11 (0-59)	75	116 (92-146)
Hodgkin lymphoma	5	94 (31-220)	2	35 (4-127)
Leukemia	12	95 (49-166)	84	122 (97-151)
Lymphoid[*]	1	91 (2-507)	26	123 (80-181)
Myeloid[*]	5	167 (54-389)	35	125 (87-174)
Multiple myeloma	3	88 (18-258)	37	101 (71-140)
Other cancer	27	63 (41-91)	234	102 (90-116)
Benign neoplasms	4	85 (23-218)	11	88 (44-157)
Blood disorders	1	22 (1-121)	27	111 (73-161)
Mental disorders	3	23 (5-66)	74	71 (56-89)
Allergic, endocrine & metabolic disease	3	10 (2-28)	217	84 (73-96)
Nervous system disease	13	70 (37-119)	198	112 (97-129)
Circulatory disease	434	67 (61-74)	3323	100 (96-103)
Nonmalignant respiratory disease	21	33 (21-51)	582	91 (84-99)
Digestive disease	26	32 (21-47)	226	80 (70-91)
Genitourinary disease	7	23 (9-47)	142	92 (77-108)
External causes	216	63 (55-72)	328	92 (82-102)
Other known	80	85 (67-105)	267	88 (78-99)
Unknown		66(46)		

[*]Lymphoid and myeloid leukemia: follow-up period 1968/1969-2009.
[†]PY, person-years.

Table 5. Observed number of deaths (D), standardized mortality ratio (SMR) and 95% confidence interval (CI) for selected causes of death among hourly workers, by years worked and years since hire, men and women combined (1943/1944-2009), 8 plants

	Worked <10 years				Worked ≥10 years			
	<20 years since hire		≥20 years since hire		<20 years since hire		≥20 years since hire	
	(PY[†]=211,971)		(PY=134,797)		(PY=81,618)		(PY=181,106)	
Cause	D	SMR (95%CI)	D	SMR (95%CI)	D	SMR (95%CI)	D	SMR (95%CI)
All causes	621	62 (57-67)	2924	100 (96-103)	371	62 (56-68)	4556	96 (93-99)
All cancer	91	56 (45-69)	801	106 (99-114)	93	80 (65-98)	1284	101 (96-107)
Esophagus	0	0 (0-95)	19	97 (58-151)	5	152 (49-354)	34	94 (65-132)
Pancreas	4	51 (14-131)	40	101 (72-138)	1	16 (0-88)	75	118 (93-148)
Lung	26	64 (42-94)	298	119 (106-133)	36	99 (69-137)	412	93 (84-102)
Bladder	1	34 (1-192)	17	97 (56-155)	1	43 (1-242)	51	148 (110-195)
Kidney	3	81 (17-237)	20	111 (68-172)	1	34 (1-192)	27	90 (60-131)
Non-Hodgkin lymphoma	0	0 (0-65)	21	85 (53-130)	1	27 (1-151)	54	136 (102-177)
Hodgkin lymphoma	2	56 (7-201)	1	45 (1-253)	3	176 (36-516)	1	29 (1-159)
Leukemia	6	74 (27-161)	24	93 (60-139)	6	133 (49-290)	60	139 (106-179)
Lymphoid[*]	1	167 (4-929)	6	79 (29-172)	0	0 (0-922)	20	149 (91-231)
Myeloid[*]	5	278 (90-648)	12	111 (57-194)	0	0 (0-335)	23	134 (85-201)
Multiple myeloma	0	0 (0-194)	13	95 (51-162)	3	200 (41-584)	24	105 (67-157)
Nervous system disease	10	79 (38-145)	81	117 (93-146)	3	50 (10-146)	117	109 (90-131)
Nonmalignant respiratory disease	12	30 (16-53)	228	95 (83-108)	9	38 (18-73)	354	89 (80-99)

[*]Lymphoid and myeloid leukemia: follow-up period 1968/1969-2009.
[†]PY, person-years.

Table 6. Total number (N) of cases (C), number (%) exposed to monomers, median (interquartile range, IQR) ppm-years of estimated exposure among cases exposed to each monomer for diseases included in Cox regression internal analyses

		Butadiene		Styrene	
	Total N	C (%) exposed	Median ppm-years (IQR)	C (%) exposed	Median ppm-years (IQR)
Cancers					
Esophagus	71	58 (82)	103 (42-285)	60 (85)	42 (7.8-55)
Pancreas	155	112 (72)	99 (29-320)	124 (80)	29 (4.4-61)
Lung, all	915	674 (74)	72 (20-226)	734 (80)	20 (4.2-44)
Lung, women	133	56 (42)	12 (2-58)	57 (43)	6 (0.8-22)
Lung, men	782	618 (79)	81 (25-236)	677 (87)	16 (5-45)
Bladder	95	76 (80)	91 (36-382)	79 (83)	36 (5.5-65)
Kidney	71	52 (73)	68 (28-212)	54 (76)	28 (4.5-42)
Non-Hodgkin lymphoma	110	76 (69)	121 (19-335)	86 (78)	19 (6.0-60)
Leukemia	132	103 (78)	121 (34-364)	109 (83)	34 (8.4-61)
Lymphoid leukemia	52	39 (75)	225 (45-425)	42 (81)	45 (8.6-69)
Myeloid leukemia	67	53 (79)	70 (26-230)	56 (84)	26 (5.4-49)
Multiple myeloma	60	40 (67)	111 (34-395)	43 (72)	34 (2.8-78)
Hodgkin lymphoma	17	9 (53)	79 (17-120)	10 (59)	4.9 (2.3-11)
Sinonasal cancer	3	3 (100)	16 (1.1-41)	3 (100)	2.9 (0.3-3.2)
Nervous system disease	275	174 (63)	65 (16-201)	187 (68)	16 (3.1-44)
Respiratory system disease	697	486 (70)	105 (30-285)	520 (75)	30 (5.4-53)
All subjects	22,785	7,268 (32)	77 (21-242)	7,889 (35)	16 (4.0-48)

Table 7. Standardized mortality ratio (SMR) for selected diseases, with observed number of deaths (D) and 95% confidence interval (CI), for workers unexposed to butadiene and for workers exposed to butadiene; rate ratio (RR), with total number of cases (C) and 95% CI, for any compared to no exposure to butadiene; and p-value for exposure-response trend with ppm-years of butadiene

	SMR, unexposed to butadiene (PY[†]=286,782)		**SMR, exposed to butadiene (PY=515,378)**		**RR[‡], exposed versus unexposed to butadiene**		**Exposure-response[‡]**
	D	SMR (95% CI)	D	SMR (95% CI)	C	RR (95% CI)	p-value for trend
Cancers							
Esophagus	12	69 (36-120)	56	102 (77-132)	71	1.28 (0.66-2.46)	0.797
Pancreas	39	85 (61-116)	101	101 (82-122)	155	1.08 (0.72-1.62)	0.277
Lung, all workers	222	88 (77-101)	626	92 (85-100)	915	1.07 (0.91-1.26)	0.868
Women	69	86 (67-108)	54	202 (152-264)	133	1.97 (1.33-2.90)	0.969
Men	153	86 (73-100)	572	88 (81-95)	782	0.93 (0.78-1.11)	0.962
Bladder	15	88 (49-145)	59	116 (89-150)	95	1.36 (0.78-2.38)	0.0003
Kidney	18	94 (56-149)	43	91 (66-122)	71	0.90 (0.51-1.59)	0.320
Non-Hodgkin lymphoma	22	72 (45-109)	63	97 (74-124)	110	0.85 (0.53-1.34)	0.898
Leukemia, total	24	80 (51-118)	87	123 (99-152)	132	1.39 (0.87-2.21)	0.014
Lymphoid[*]	8	106 (46-209)	23	117 (74-176)	52	1.09 (0.54-2.24)	0.007
Myeloid[*]	12	99 (51-174)	36	132 (93-183)	67	1.47 (0.77-2.84)	0.602
Multiple myeloma	17	116 (68-186)	33	96 (66-135)	60	0.72 (0.39-1.33)	0.708
Nervous system disease	101	109 (88-132)	174	103 (88-119)	275	0.80 (0.60-1.07)	0.077
Nonmalignant respiratory disease	211	79 (69-90)	486	82 (74-89)	697	1.03 (0.85-1.25)	0.055

[*]Lymphoid and myeloid leukemia: follow-up period for SMRs, 1968/1969-2009.

[†]PY, person-years.

[‡]Adjusted for age at outcome occurrence, year and age at hire, race, gender, plant and ever-hourly status.

Table 8. Standardized mortality ratio (SMR) for selected diseases, with observed number of deaths (D) and 95% confidence interval (CI), for workers unexposed to styrene and for workers exposed to styrene; rate ratio (RR), with number of cases (C) and 95% CI, for any compared to no exposure to styrene; and p-value for exposure-response trend with ppm-years of styrene

	SMR, unexposed to styrene (PY[†]=228,516)		SMR, exposed to styrene (PY=573,644)		RR[‡], exposed versus unexposed to styrene		Exposure-response[‡]
Cancers	D	SMR (95% CI)	D	SMR (95% CI)	C	RR (95% CI)	p-value for trend
Esophagus	11	85 (42-152)	57	96 (73-125)	71	1.2 (0.59-2.47)	0.994
Pancreas	29	78 (52-113)	111	102 (84-123)	155	1.29 (0.80-2.08)	0.212
Lung, all	165	84 (71-97)	683	93 (87-101)	915	1.10 (0.91-1.34)	0.914
Women	68	89 (69-113)	55	179 (135-233)	133	1.55 (1.01-2.37)	0.874
Men	97	74 (60-90)	628	90 (83-97)	782	1.00 (0.80-1.24)	0.973
Bladder	13	93 (50-160)	61	113 (87-146)	95	1.23 (0.66-2.28)	0.004
Kidney	15	99 (55-163)	40	90 (66-120)	71	0.68 (0.37-1.26)	0.663
Non-Hodgkin lymphoma	16	64 (36-104)	69	98 (77-125)	110	1.02 (0.59-1.76)	0.854
Leukemia	19	76 (46-119)	92	121 (97-148)	132	1.32 (0.77-2.25)	0.116
Lymphoid*	6	97 (36-211)	25	119 (77-176)	52	1.08 (0.48-2.44)	0.046
Myeloid*	9	92 (42-174)	39	132 (94-181)	67	1.45 (0.69-3.08)	0.877
Multiple myeloma	15	123 (69-203)	35	95 (66-132)	60	0.67 (0.34-1.31)	0.856
Nervous system disease	88	112 (90-138)	187	102 (88-118)	275	0.73 (0.53-1.00)	0.132
Nonmalignant respiratory disease	177	81 (70-94)	520	81 (74-88)	697	0.97 (0.78-1.19)	0.145

*Lymphoid and myeloid leukemia: follow-up period for SMRs, 1968/1969-2009.

[†]PY, person-years.

[‡]Adjusted for age at outcome occurrence, year and age at hire, race, gender, plant and ever-hourly status.